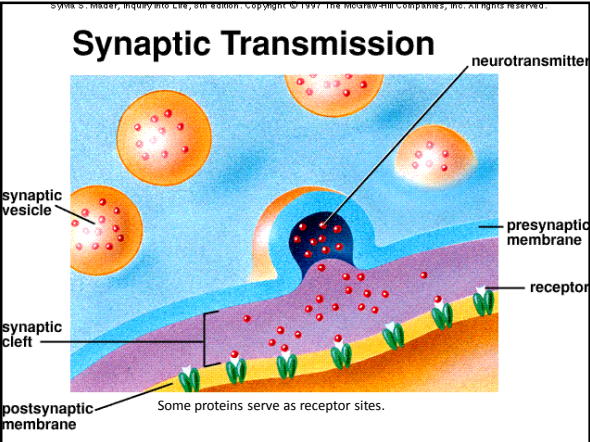
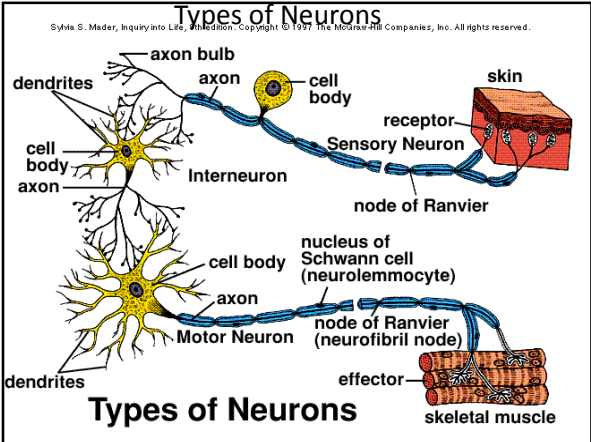
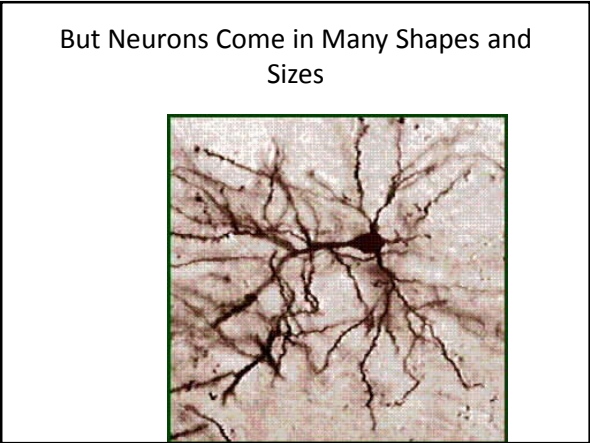
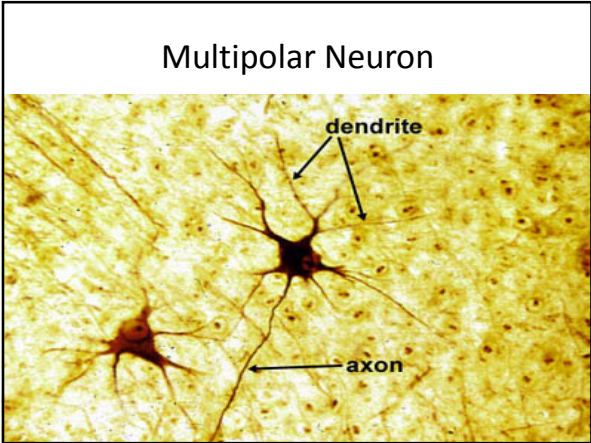
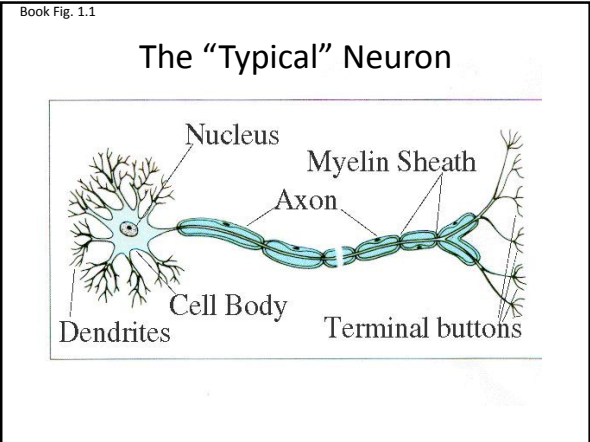


Cells of the Nervous System:

Neurons: cells that receive & send messages
 Glia: cells which support neuron functioning in many ways



Best Known Neurotransmitters
(study handout linked to syllabus)

- Acetylcholine (ACh)
- Norepinephrine (NE)
- Dopamine (DA)
- Serotonin or 5-Hydroxytryptamine (5HT)
- GABA
- Glutamate-most widespread excitatory transmitter

Released neurotransmitter must bind to specially shaped receptors like a key fitting into a lock. We now know there are multiple subtypes of receptors for each neurotransmitter.

Then the transmitter must be removed from the synapse either by reuptake or enzymatic breakdown.

Best Known Neurotransmitters
(FYI only – not completely up-to-date list of the number of identified receptor subtypes)

- Acetylcholine (ACh) (7 receptor subtypes)
- Norepinephrine (NE) (11 receptor subtypes)
- Dopamine (DA) (5 receptor subtypes)
- Serotonin (5HT) (14 receptor subtypes)
- GABA (2 receptor subtypes)
- Glutamate (10 receptor subtypes)

- These numbers are changing with new discoveries

Here's some background on ACh before we cover an Example of a neurotransmitter related disorder

Acetylcholine (ACh)

- neurons using ACh are known as "cholinergic neurons".
- Examples:
 - motor neurons
 - parasympathetic neurons
 - many CNS neurons (in cortex, basal ganglia, hippocampus, brainstem)
 - Different ACh receptor types on muscle (nicotinic) than in the nervous system (muscarinic)
 - acetylcholinesterase breaks down released ACh

Neuromuscular (nerve to muscle) Junction - depends on ACh
Histology Lab Part 6: Slide 20

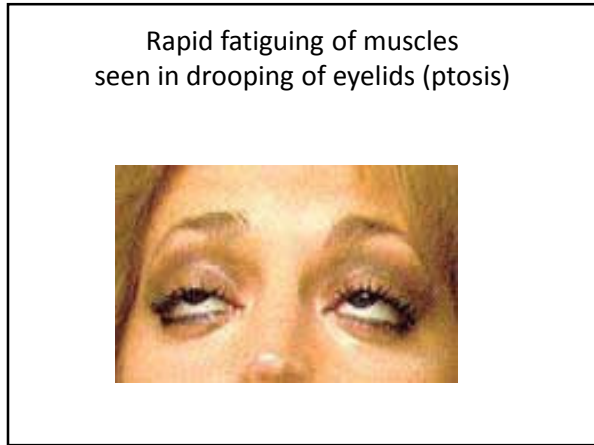
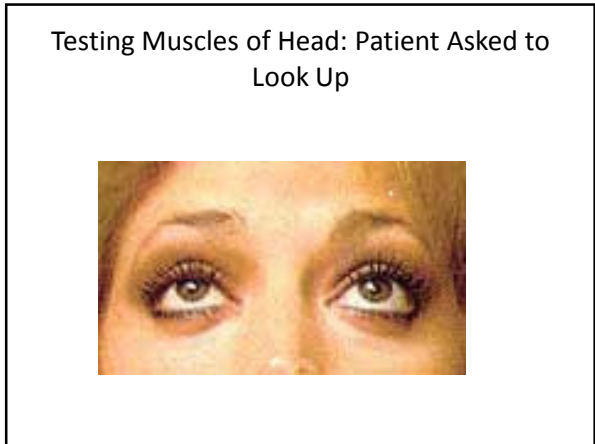
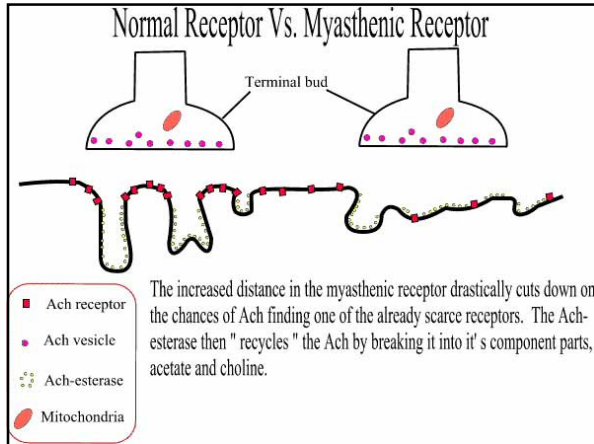
Synaptic endfoot of a motor neuron synapsing on a muscle fiber

note – some references call this the myoneural junction but that seems backwards

"weakening" "grave or serious"

Myasthenia Gravis: Most Common Neuromuscular Disease (>36,000 in US)

- abnormal muscle fatigability & weakness
- usually slowly progressive, affecting muscles of head first
- autoimmune disease- develop antibodies which attack ACh receptors on muscles, impairing the motor commands to muscle
- Most often strikes younger women and older men



- ### MG Diagnostic Tests
- Edrophonium (Tensilon) test –administration of short-acting **anti**-cholinesterase sustains the effect of Ach on receptors so usually produces brief improvement if person has MG (see next slide)
 - ~75% have detectable serum antibodies
 - Nerve conduction studies show normal conduction in the nerve; electromyogram shows initially normal muscle response which decreases with each response
 - Chest xray may show thymoma, ~70% have overactivity of thymus

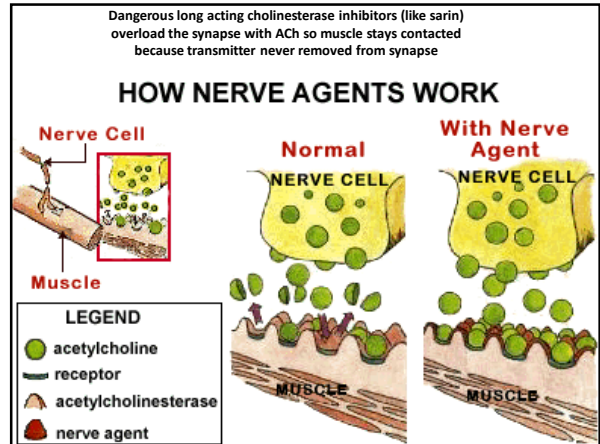
- Myasthenic rabbit can't lift ears until given an anticholinesterase drug.
- Myasthenic dog can't lift head due to weakness.

Click the "X" in the upper right hand corner of this window to return.

Please do not copy or reproduce this picture in any way.

- ### MG Treatments
- Increase ACh levels with an **anti**-cholinesterase drug (a drug which inhibits the enzyme that would normally breakdown ACh, thus prolonging ACh's ability to stimulate remaining ACh receptors)
 - Decrease the attack by the immune system:
 - thymectomy
 - corticosteroids & immunosuppressant drugs
 - plasma exchange to remove antibodies
 - IV immune globulin

- But using just the right amount of anticholinesterase can be tricky
- *Too much* neurotransmitter action at a synapse can be as bad as too little
- The proper balance is key to normal functioning
- A strong anticholinesterase drug can thus be used as a lethal poison!



- What if you have enough transmitter and healthy receptors, but the transmitter is not *released* when the nerve impulse arrives at the axon ending?

- ### Botulism Poisoning (~110 cases/yr)
- Botulinum toxin produced by bacteria *Clostridium botulinum* or its spores, incredibly potent, easily absorbed from GI tract, and then distributed by blood everywhere except CNS
 - **Interferes with the release** of ACh, causing paralysis & preventing ACh autonomic effects (causes dry mouth, constipation)
 - Beginning signs of paralysis: double or blurry vision, droopy eyelids, weak voice/cry, slurred speech, difficulty swallowing, weakness & decreased muscle tone. Can progress to complete paralysis & respiratory failure.
 - Treatment with antitoxin can prevent progression but recovery of already affected ACh neurons takes weeks-months of recovery

- Botulism poisoning is bad because you are at risk of all motor neurons and all parasympathetic neurons being unable to function (deadly).
- But what if you could cause this effect (inability to release ACh) at just select synapses?

- ### Botox
- Selective localized injections of an artificial form of botulinum toxin now used to *treat* excess or unwanted muscle contraction:
 - Strabismus (crossed eye/lazy eye)
 - Blepharospasm (involuntary eye closing)
 - Cervical dystonia & other focal spasms
 - Hemifacial spasms
 - Spasticity after CNS damage (e.g. cerebral palsy, stroke, multiple sclerosis)
 - Muscle contractions causing wrinkles
 - Also:
 - Experimental treatment for migraine

Woman Suffering Eyelid Spasms




After botox in eye closing muscles

Cervical Dystonia



- The neuromuscular junction would also malfunction if motor neurons released ACh all the time (instead of just when there is a nerve impulse).

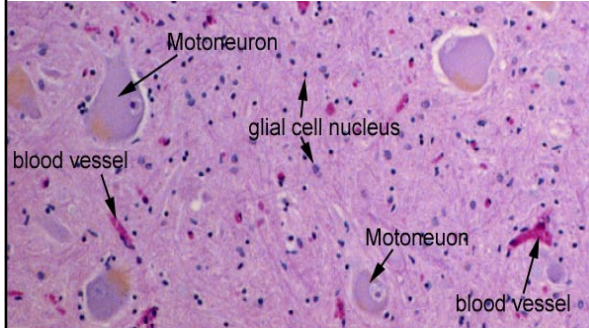
Black Widow Spider Venom



Venom of spider triggers release of ACh without action potential, causing muscle spasms that could interfere with breathing


- ### Glial Cells (“supporting cells”)
- 5-10X more numerous than neurons
 - make up about half of brain weight
 - several distinct types
 - growing evidence of multiple roles

Neurons and Smaller Glia



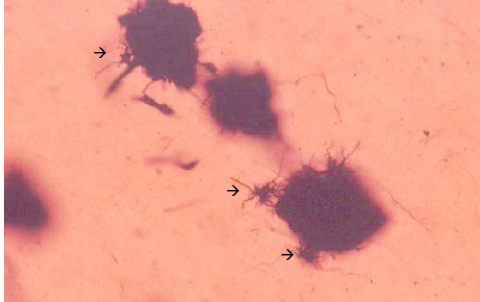
Labels: Motoneuron, glial cell nucleus, blood vessel

Astrocytes (most common)



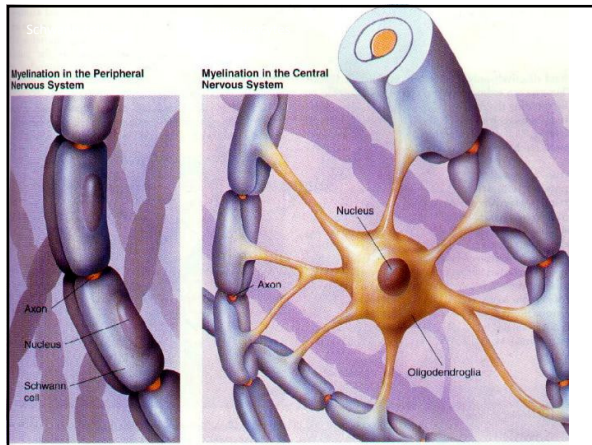
- separate synapses
- surround CNS capillaries, adding to blood-brain barrier
- transfer materials to & from neurons
- clean up excitatory transmitter glutamate
- produce growth factors
- can multiply to form scar tissue or tumors
- may even communicate?

Astrocytes "Tending" Neurons

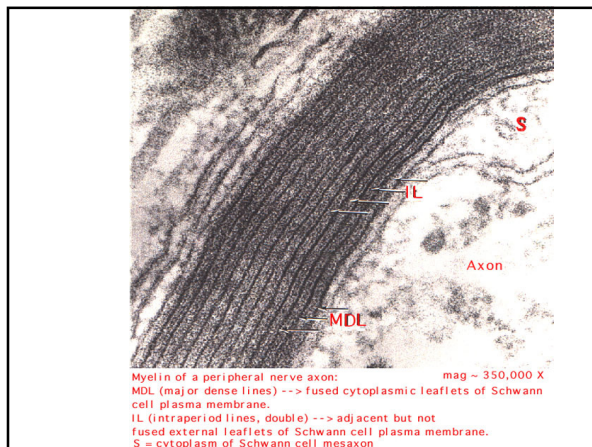
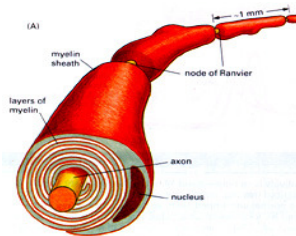


Oligodendrocytes

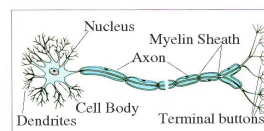
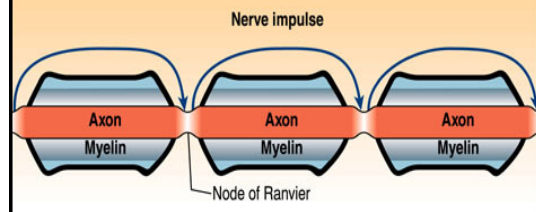
- form myelin sheaths on CNS neurons, greatly increasing the speed of nerve impulse conduction down the axon
- form thin coat on unmyelinated ones
- produce nerve growth factor
- Schwann cell is the PNS counterpart



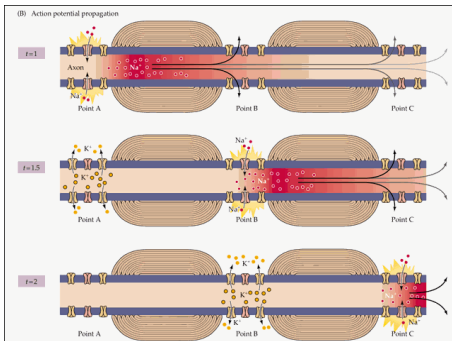
Schwann Cells



Normal Conduction of Myelinated Nerve Fibers



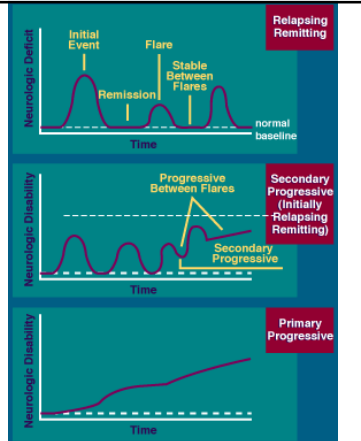
In a Myelinated Neuron:
Saltatory Conduction



Multiple Sclerosis: Another Autoimmune Disease

- Immune system attacks white matter in **CNS**, causing patches of demyelination in ~400,000 in US (2/3 are women)
- Where myelin is lost, hard plaques of scar tissue form & eventually neurons may die
- Symptoms depend on which neurons lose myelin but always **multiple symptoms (clinically diagnosed)**
- Most experience periodic attacks/relapses (days) & then remissions (months) which get progressively worse over the years
- Most common serious CNS disease of young adults; most common autoimmune disorder in US& UK

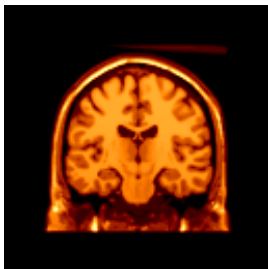
Different patterns
Of progression



Some Possible Symptoms

- Visual problems
- Weakness
- Balance problems
- Sensory abnormality
- Ataxia (incoordination)
- Cognitive difficulties
- Bladder/bowel problems
- Fatigue
- Heat often aggravates symptoms, as does illness or stress

Normal White Matter (see p.17)



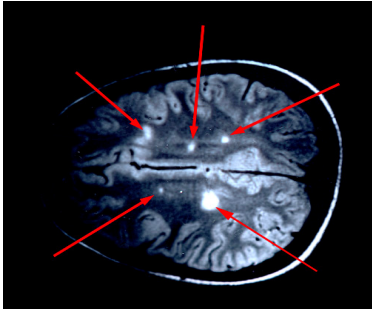
Loss of White Matter in MS



Dark patches where there would normally be white matter

In this MPI contrast is reversed so white matter looks dark and bright spots are patches of myelin loss.

Demyelination Seen in MRI

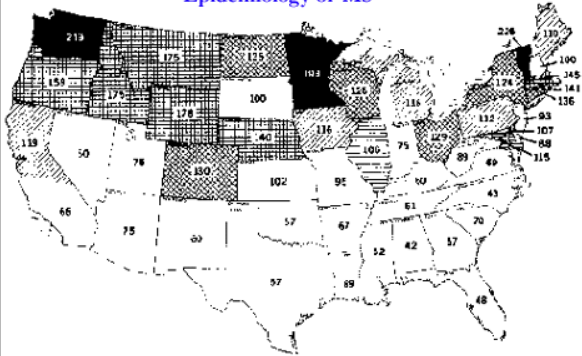


What Causes MS?

- Prevalence correlated with distance from equator (e.g. more common in northern states) – risk related to where you spent your childhood
- Perhaps northern regions associated with higher exposure to illness during cold months? Perhaps certain bacteria/virus carry proteins similar to a myelin protein? (e.g. Herpes and Chlamydia)
- A large scale study demonstrated another critical factor- sunlight exposure/Vitamin D supplements seems to have a protective effect – south gets more sun
- Less common in Blacks, Asians, Native Americans; shows some tendency to run in families (role of genetics), but identical twins only have 25-30% concordance.

Cases per 100,000 population

Epidemiology of MS



MS Treatment Approaches

- Immunomodulator interferon-beta and
- “Myelin decoy” glatiramer recommended for every case of relapsing-remitting MS to decrease relapses & slow progression
- Anti-inflammation corticosteroids (prednisone, prednisolone, dexamethasone) to shorten attacks
- Avoid stress & illness; get regular vaccines
- Treat the symptoms (fatigue, spasticity, pain, bladder problems)

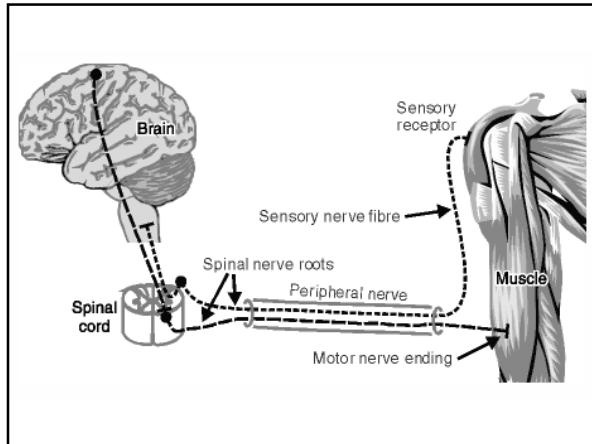
How about the myelin in the PNS?

Consider this:

- You’ve recently had the flu or some other infection (60%), or you’ve had a vaccination. You notice some tingling & numbness in your feet & your legs seem to be getting weaker (60% can’t walk). Over a period of **hours** (or up to 2 weeks) the weakness & loss of ability to move moves up your body. If it gets high enough you may not be able to breathe (20-30%) swallow, or speak & may have bilateral facial paralysis. One in 20 will die.

Guillain-Barre Syndrome

- Rapid, ascending, usually symmetrical **PNS** demyelination in ~ 2/100,000 pop.
- Loss of motor function most obvious sensory and autonomic losses also occur
- Can be a medical emergency- 25% need artificial respiration
- Probably a temporary autoimmune disorder; majority have recently had an infection, vaccination, or surgery
- Some begin recovery within weeks, others months. 70-75% full recovery
- Aka “acute inflammatory demyelinating polyneuropathy”



- Plasma exchange & immune globulins used to shorten disease
- Physical therapy to maintain muscles

Figure 1a

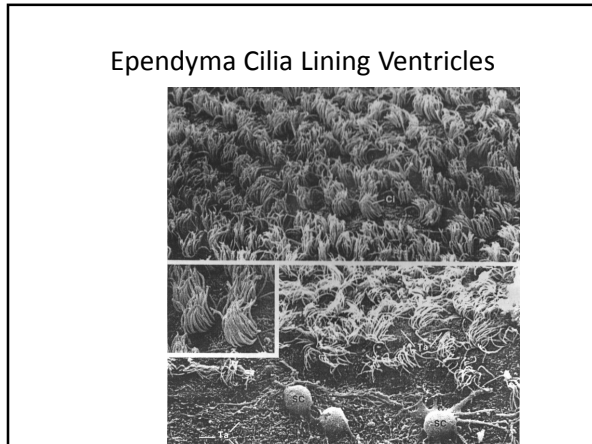
Figure 1b

Microglia

- Small glia which are mobile phagocytes (scavenger cells cleaning up debris)
- May play a key role in neurodegenerative diseases - "activated" microglia may attack neurons in AIDS, Alzheimer's, MS
- Contribute to scar tissue formation

Ependyma

- line the ventricles/canals
- have cilia to help circulate CSF
- may transport materials between CSF & neurons



Glia Clinical Notes

- Multiplying of glia to form scar tissue ("gliosis") can irritate nearby neurons: important cause of post-traumatic/focal epilepsies.
- 60% of primary brain tumors are **gliomas**, e.g.
 - Astrocytomas-most common type of tumor
 - Most dangerous form: glioblastoma multiforme
 - Oligodendroglioma
 - CNS lymphomas (microglia)
 - Schwannomas – e.g. acoustic schwannoma
 - Ependymoma

Primary Brain Tumors/Neoplasms

- Usually due to abnormal growth of cells other than neurons
 - ~20% Meningiomas - benign, encapsulated growth of meninges
 - ~60% Gliomas - infiltrating, usually malignant multiplication of glial cells varies (Grade I-IV and glioblastoma)
- Possible causes: exposure to toxic chemicals or excessive radiation, impaired immune function, heredity

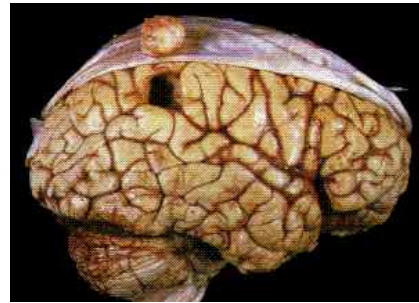
Brain Tumors ~100,000/yr in US

- ~17,000 originate in brain (“primary brain tumors”)
- Remainder are “secondary” or metastatic tumors, seeded by cancer cells carried in blood stream from other cancers (breast, lung, kidney, skin, etc.)

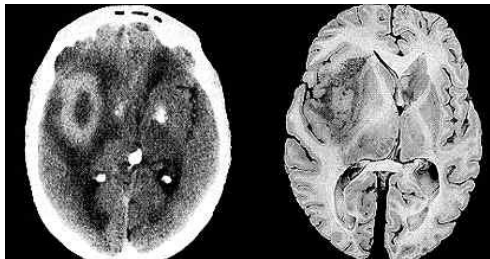
Brain Tumors continued

- Most tumors occurring in adulthood are “supratentorial” (in cerebral hemispheres)
- Most tumors in children are “infratentorial” (below tentorium, in brainstem). The single most common is a medulloblastoma.
- Tumor problems: **compression of brain, increased ICP**, sometimes may impair CSF flow or endocrine controls, infiltration into brain tissue may disrupt normal connections.

Meningioma



Astrocytoma



Metastatic Tumors



Advances in Treatment

- Neuroimaging of tumor and blood vessels
- Surgical microscope + microsurgery tools
- Surgical lasers
- Stereotactic radiosurgery with gamma knife
- Ultrasonic aspirator
- Radiosensitizing drugs (enhances radiation therapy)
- Radioactive implants
- Implanted chemotherapy wafers
- <http://www.5min.com/Video/Brain-Tumor-Surgery-114223633>

- The functioning of the cells of the nervous system can also be altered by a wide variety of outside agents – for example - viral, bacterial or fungal infections or toxic substances. The following are just a few related disorders.

Classic Creutzfeldt-Jakob Disease (CJD)

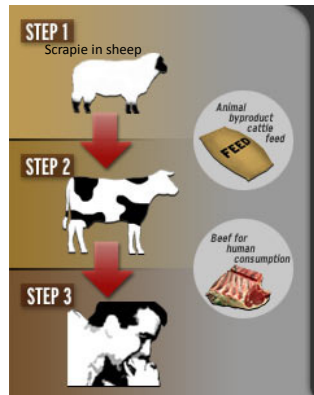
- Rare (1/1,000,000) progressive dementia, motor problems, and death
- In most cases cause is unknown, but some may be caused by exposure to tissue (transplants, human growth hormone injections, contamination from previous brain surgery on infected patient). A few (5-10%) cases are familial (genetic).
- May have a long, long incubation period; usually seen in older adults
- Caused by tiny abnormal forms of proteins called prions which are very resistant to inactivation

Bovine Spongiform Encephalopathy (BSE)



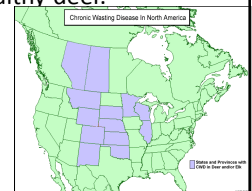
- Related animal disease transmitted by cattle eating feed containing tissue from infected animals (“mad cow disease”)
- 1996 – evidence that BSE could cause a faster “variant CJD” in humans
- 1/2001 – FDA banned blood donations from those who lived in BSE countries or anyone associated with CJD
- Similar transmissible encephalopathy has been seen after eating squirrel/mink brains in Kentucky

- Transmissible spongiform encephalopathies



Chronic Wasting Disease in US (11 states so far) Deer

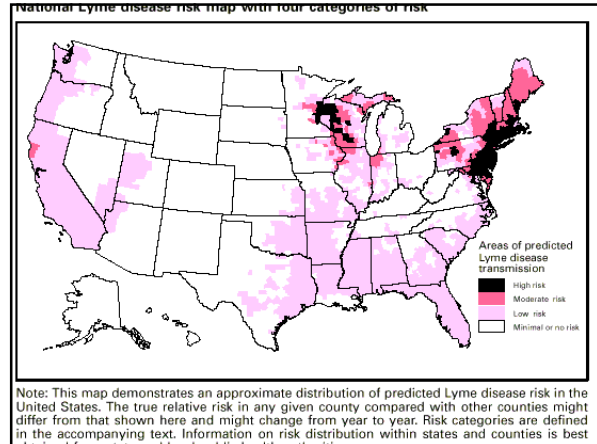
- Animal disease resembles BSE
- Thusfar those states not showing ↑CJD, so CWD may not be easily transmissible to those consuming infected deer, but hunters advised to stay clear of wasted, unhealthy deer.



Lyme Disease

(150,000 cases since 1982)

- Infected by bacterium *Borrelia burgdorferi* transmitted from deer or mice to humans by ticks
- untreated can cause arthritis and neurological problems like
 - Cranial nerve problems like Bell's palsy
 - Peripheral neuropathy symptoms (tingling, weakness)
 - Meningitis or encephalitis
 - Headache and extreme fatigue
 - Concentration or memory problems
 - Disorientation and cognitive decline



Tick Bite

- Adult tick
- Must be in place 24-36 hrs to transmit disease



Bull's Eye Rash 7-14 days later



- Feel tired, achey, low grade fever
- Treat with antibiotics

Some Other CNS Infections

- Viral
 - May be pantropic (general infections of many tissues like mumps or herpes) or neurotropic (specific affinity for nerves).
 - Example: **viral encephalitis** – many varieties (St. Louis, Equine, HIV) – virus spreads to brain itself with high risk of mortality or disability
 - Common forms spread from animals to humans by mosquitos

Rabies – a neurotropic infection

- Virus is picked up by nerve endings at the site of the bite & slowly (2 weeks-6 months) travels to CNS via retrograde transport up the axon. If the virus reaches the CNS before vaccination it is almost invariably fatal.
- Symptoms may appear in 2 forms: “furious rabies” - hyperexcitable, irritable, muscle pain and spasms, may viciously bite at anything (like Cujo or Old Yeller), or “dumb rabies” - lethargy progressing to paralysis & coma